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> ONE MONTH, ONE PROTEIN <

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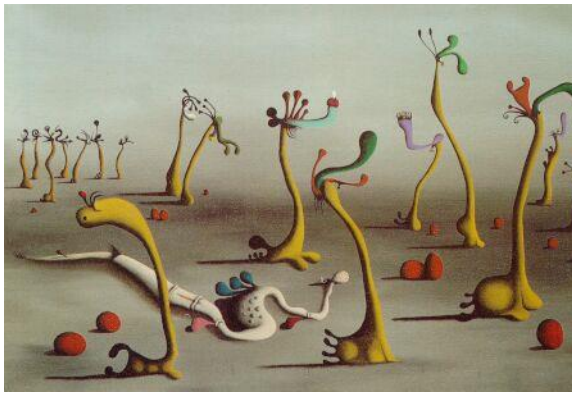
versatile

Vivienne Baillie Gerritsen

You cannot beat versatility. Whichever way you look at it, versatility strengthens, opens doors, widens horizons. Many notorious people have been endowed with multiple talents. Author of the hugely popular book on human behaviour "The Naked Ape", Desmond Morris has not only spent a life as a zoologist and a writer but also as a surrealist painter. Dora Maar, in her days, was a well-known photographer as she was a poet and a painter. Le Corbusier, too, gained recognition for his architecture as he did for his furniture design and sculptures. Leonardo da Vinci also comes to mind – as many others do too. Of course, you do not need to be famous to be multi-talented. You do not need to be human, either. You can even be a protein. While many proteins, through the course of their existence, are quite content to have one role, others may be endowed with more. One such protein is transglutaminase 2, whose achievements are so varied that it even ends up being involved in opposing events, such as cell growth and cell death.



Disturbance In The Colony, by Desmond Morris

Courtesy of the artist, writer & zoologist

Transglutaminases were discovered in New York in the 1950s by the neurochemist Heinrich Waelsch who, at the time, was interested in neurotransmitters – namely, glutamates – and how they bind to proteins at the postsynaptic level. Shortly before the structure of DNA had been deciphered and the intimacy of proteins had been understood, Waelsch, and a few fellow researchers, not only described how transglutaminases probably acted on the molecular level but also how they may be involved in neural pathological processes. To sum things up briefly, transglutaminases create bridges, or crosslinks, between proteins via a process known as transamidation, during which glutamine residues (in one protein) are linked to lysine residues (in the other) by way of a particularly solid bond. One transglutaminase, however, is proving to be far more resourceful than its family members: transglutaminase 2, or TG2.

The great majority of transglutaminases are indeed involved in a variety of biological activities that they promote by crosslinking proteins. One example is coagulation factor XIII, a transglutaminase responsible for crosslinking proteins known as fibrins, ultimately leading to the clotting of blood at the site of a wound. Transglutaminase 2 also happily crosslinks proteins via transamidation, but it can also act as a GTPase. Thus armed, TG2 has been shown to be involved in biological processes as diverse as cell adhesion, cell motility, cell signalling as well as the erection of cellular scaffolds – all of which happen to be essential steps in cell growth and development. But also in cell damage and cell death.

As could be expected from an enzyme involved in such a wide span of biological activities, besides being present in almost all types of tissue, TG2 can be either extracellular or intracellular where it is found in the cell cytosol, the nucleus, the mitochondrion and endosomes. The omnipresence of TG2 both in tissues and

various cell compartments could help to explain the multiplicity of its talents – which could be influenced, or brought about, by its surroundings.

Although TG2 multiplicity continues to confound researchers, the discovery that the enzyme takes part in events as opposing as cell growth and cell death is perhaps even more astounding. As an illustration, during apoptosis, extracellular TG2 is known to promote the crosslinking of two proteins – fibronectin and integrin – to form a strong extracellular scaffold which surrounds the dying cell while preventing its insides from leaking out. Another surprising find is TG2's involvement in modifying histones – more precisely histone H3 – and its subsequent influence on gene expression. Histones are proteins which participate in condensing and protecting DNA in the nucleus. When certain genes need to be expressed, the protective histones must release their grip, so to speak, so that gene transcription can occur. TG2 unfastens H3's hold by way of a chemical modification known as serotonylation, where serotonin is popped onto a glutamine residue on H3.

Could TG2's involvement in so many biological activities be explained on a structural level? Perhaps. TG2 exists in two distinct conformations – open and closed – depending on the presence and the concentration of Ca^{2+} and GTP. When Ca^{2+} levels are low, TG2 binds GTP causing the enzyme to fold up onto itself and adopt the closed form. In this conformation, TG2 is unable to bind to its substrate – glutamine – to follow through with transamidation. Despite this, the enzyme is able to perform GTP-dependent functions such as phosphorylation for example. When Ca^{2+} levels increase, under environmental stress for example, the affinity for GTP-binding weakens and TG2 opens up thus presenting its substrate-binding site, ready for transamidation.

TG2 could thus be capable of multiple roles thanks to the uncharacteristically large structural difference between its closed and open forms, its concomitant binding to Ca^{2+} and GTP, and the capacity to remain active in both conformations. Besides this surprising state of events, scientists have also had to come to terms with the almost disturbing notion that TG2 displays opposing effects – like cell death and cell survival – within the same physiological system, so much so that the case of this enzyme has been compared to that of Robert Louis Stevenson's Dr Jekyll and Mr Hyde. Endowed with so many talents and ubiquitous, it is hardly surprising to learn that TG2 is expected to take part in several diseases – among which, as Waelsch had surmised, neurodegenerative diseases like Alzheimer, Parkinson, Huntington and perhaps even multiple sclerosis, besides certain forms of cancer and autoimmune disorders such as celiac disease. Understanding the molecular structure of TG2 in each of its two conformations will help design drugs which, much like the multi-faceted enzyme, are expected to have more than just one pharmacological effect.

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